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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/678,851	10/04/2000	Robin E. Offord	GRFN-026/03US	1974

7590 06/25/2003

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EXAMINER
CELSA, BENNETT M

ART UNIT	PAPER NUMBER
1639	12

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

file copy

Office Action Summary

Application No.	Applicant(s)
09/678,851	Offord et al.
Examiner	**Art Unit**
Bennett Celsa	1639

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 13, and 18-24* is/are pending in the application.

4a) Of the above, claim(s) *2, 3, 5-8, 18, 19, and 21-24* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4, 13, and 20* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 1-8, 13 and 18-24 are currently pending.

Claims 1, 4, 13 and 20 are under consideration.

Claims 2-3, 5-8, 18, 19 and 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Election/Restriction

1. Applicant's election of Group I (claims 1-8, 13 and 18-24) and n-nonayl Rantes (2-68) [R1 is CH3-(CH2)7-C(=O)-Rantes e.g. n is 7 and X is -C(O)-] which reads on claims 1, 4, 13 and 20, in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 2-3, 5-8, 18, 19 and 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 4, 13 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Compound and composition claims 1 and 13 (and claims dependent thereo) lack metes and bounds regarding "variants" of R1-RANTES (2-68) in which "variants" are defined to be any RANTES antagonist which has at least 40% sequence homology to RANTES (2-68) (67 amino acids of seq. Id. 2) which results from any substitution and/or deletion and/or insertions of 1-20 or more amino acids of seq. 2 (up to 50% or @ 33 amino acids of seq. 2). See specification page 4. The amino acids substitutions/insertions include both conservative and non-conservative amino acids and are not limited to the 20 naturally occuring amino acids but can include unnatural amino acids. The claims do not recite a common peptidic core structure necessary to elicit a common utility e.g. RANTES antagonism; nor is the degree of RANTES antagonism and means of measuring thereto claimed. Additionally, the specification does not define the program and parameters thereof (e.g. acceptable gaps etc.) which is to be used to measure "homology". Accordingly, there is no metes and bounds regarding the ultimate "variant" RANTES SEQ. ID2. necessary to infringe not infringe the claims.

B. In claim 13 (and claims dependent thereon), the term "a disease state ... alleviated by treatment with a RANTES inhibitor" is indefinite in light of the specification definition of the term "treatment" (E.g. specification pages 6-7) e.g. as encompassing "prevention". Although applicant is free to be his/her own lexicographer, applicant's definition of "treatment" to encompass "prevention" is repugnant to the art-accepted common definitions for prevention and treatment which differentiates treatment from prevention.

5. Claims 1, 4, 13 and 20 are rejected under 35 U.S.C.112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Inadequate Written Description).

The presently claimed invention encompasses:

Compound and composition claims 1 and 13 (and claims dependent thereo) that comprise *"variants" of R1-RANTES (2-68)* in which "variants" are defined to be any RANTES antagonist which has at least 40% sequence homology to RANTES (2-68) (67 amino acids of seq. Id. 2) which results from any substitution and/or deletion and/or insertion of 1-20 or more amino acids of seq. 2 (up to 50% of seq. Id 2 or the additions/deletion insertion of up to 33 amino acids). See specification page 4. The amino acids substitutions/insertions include both conservative and non-conservative amino acids and are not limited to the 20 naturally occuring amino acids but can include unnatural amino acids (e.g. beta/gamma amino acids; modified

peptide bonds/sidechains etc.) . The claims do not recite a common peptidic core structure necessary to elicit a common utility e.g. RANTES antagonist; nor is the degree of RANTES antagonism and means of measuring thereto claimed. Additionally, the specification does not define the program and parameters thereof (e.g. acceptable gaps etc.) which is to be used to measure "homology". Accordingly, the breadth of potential R1-RANTES variant peptides encompassed by the present claims is huge and variable in chemical structure.

In support, of the broadly claimed R1-RANTES "variant" peptides described above, the specification fails to exemplify a single "variant" R1-RANTES variant peptide within the scope of the above-identified specification definition.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. In Eli Lilly, a disclosure of the sequence of rat cDNA was held not to be descriptive of the broader invention consisting of mammalian and vertebrate cDNA, although it was a species falling within the scope of those claims. Eli Lilly, 119 F.3d at 1567-68, 43 USPQ2d at 1405. In Eli Lilly, the specification and

generic claims to all cDNAs encoding for vertebrate or mammalian insulin did not describe the claimed genus because they did not set forth any common features possessed by members of the genus that distinguished them from others; nor did the specification describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they had possession of the breadth of the genus, as opposed to merely one or two such species.

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics; to demonstrate possession of the claimed generic(s).

Additionally, it is noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co*

As pointed out above, the claimed specification does not disclose any examples of "variants", which represents a broadly (e.g. both structurally and functionally) defined genus, so as to set forth any common features (peptidic core sequence) necessarily possessed by members of the "genus" that distinguish them from others; nor does the specification describe a

sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they have possession of the breadth of the genus.

6. Claims 1, 4, 13 and 20 are rejected under 35 U.S.C.112, first paragraph, because the specification, while enabling for compounds of formula R1-RANTES(2-68: seq. Id 2)and pharmaceutical compositions thereof; the specification does not reasonably provide enablement of

a. the making and use of "variants" of seq. Id. 2); and/or

b. the making and use of both R1- RANTES 2-68 variants and non-variants for "treating" disease states including (but not limited to) those recited on specification page 7 (including HIV) in which "treating" includes PREVENTION.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

a. The breadth of the claims.

b. The nature of the invention

c. The state of the prior art;

d. The level of one of ordinary skill

e. The level of predictability in the art;

f. The amount of direction provided by the inventor;

g. The presence or absence of working examples;

h. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;

See :*In re Wands* USPQ 2d 1400 (CAFC 1988):

(1-2) The breadth of the claims and the nature of the invention:

The presently claimed invention is directed to:

Compound and composition claims 1 and 13 (and claims dependent thereo) that comprise *"variants" of R1-RANTES (2-68)* in which "variants" are defined to be any RANTES antagonist which has at least 40% sequence homology to RANTES (2-68) (67 amino acids of seq. Id. 2) which results from any substitution and/or deletion and/or insertion of 1-20 or more amino acids of seq. 2 (up to 50% of seq. Id 2 or the additions/deletion insertion of up to 33 amino acids). See specification page 4. The amino acids substitutions/insertions include both conservative and non-conservative amino acids and are not limited to the 20 naturally occuring amino acids but can include unnatural amino acids (e.g. beta/gamma amino acids; modified peptide bonds/sidechains etc.) . The claims do not recite a common peptidic core structure necessary to elicit a common utility e.g. RANTES antagonist; nor is the degree of RANTES antagonism and means of measuring thereto claimed. Additionally, the specification does not define the program and parameters thereof (e.g. acceptable gaps etc.) which is to be used to measure "homology". Accordingly, the breadth of potential R1-RANTES variant peptides encompassed by the present claims is huge.

Additionally, in claim 13 (and claims dependent thereon) are drawn to pharmaceutical compositions for administration to "mamamals" having "a disease state ... alleviated by **treatment** with a RANTES inhibitor", in which "treatment" is defined to encompass (E.g. specification pages 6-7) "prevention"

(3 and 5) *The state of the prior art and the level of predictability in the art:*

The presently claimed RANTES compounds and compositions thereof rely on their ability, as chemokine receptor antagonists, to efficaciously bind receptors present on cell surfaces (E.g. macrophage, lymphocytes etc.) in order to achieve the desired pharmacological response (e.g. "treatment" of HIV1 in infected individuals). E.g. see specification pages 1-2.

However, ligand (e.g substrate/inhibitor) /receptor binding is unpredictable insofar that minor changes in substrate structure may result in an inactive substrate analogue due to the stereospecific requirements of receptor binding. For example, the significance of particular amino acids and sequences for different aspects of biological activity,with respect to receptors (e.g. hormones), cannot be predicted, a priori, but must be determined from case to case by painstaking experimental study (e.g., see J. Rudinger, Peptide Hormones (6/76)(University Park Press, J.A. Parsons, Ed.) pages 1-7 at page 6) since the mere changing of a single amino acid with a so-called "conservative" amino acid may serve to unpredictably remove biological activity. E.g. See Rudinger at page 3, lines 12-20 where diasteromeric allo-Ile for Ile substitution in oxytocin. Additionally, in this regard, it is noted that compound claims which **lack critical or essential subject matter** (e.g. critical core structure) which is nessary to the practice of the

invention (e.g. binding a particular receptor) , but is not included in the claim(s) is not enabled (e.g. lacks utility) by the disclosure. See *Ex Parte Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441

The claimed pharmaceuticals compositions encompass the prevention of a broad array of diseases (e.g. viral diseases including HIV; rheumatoid arthritis, asthma etc. : see specification page 7) having unrelated: origin, pathologies, symptoms and degrees of recalcitrance to treatment.

Additionally, the burden of enabling the prevention of a disease (ie. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. The specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to different diseases states within the scope of the presently claimed invention, nor is guidance provided in the specification as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed composition in preventing these diseases states (E.g. HIV)..

(4) *The level of one of ordinary skill in the art:*

The level of skill would be high, most likely at the Ph.D. level.

(6-7) *The amount of direction provided by the inventor and the existence of working examples.*

The specification does not disclose any examples of "variants" which represents this broadly (structurally and functionally) defined genus so as to set forth any common features (peptidic core sequence) necessarily possessed by members of the "genus" that distinguish them from others; nor does the specification describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, i.e., that they have possession of the breadth of the genus. Regarding, prevention, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to different diseases "alleviated by treatment (e.g. prevention) with a RANTES inhibitor" including viral disease states (E.g. HIV), autoimmune diseases etc. . Nor is guidance provided in the specification as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed composition in preventing these unrelated disease states.

(8) *The quantity of experimentation needed to make or use the invention based on the content of the disclosure:*

In light of the specificity needed for receptor binding; the unpredictability regarding subtle difference between peptide substrates and effects on biological activity; the difficulty in obtaining in vivo inhibition; the amount of experimental evidence to demonstrate in vivo treatment; the unpredictability of the present art area; and the necessity of determining screening and testing protocols to demonstrate the preventive efficacy of the presently claimed invention it

would necessarily constitute undue experimentation if one wished to practice the present invention as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1, 4, 13 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,168,784. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the patent claims encompass R1-Rantes (2-68) (seq. Id. 2) compounds and compositions thereof within the scope of the present invention.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang (art unit 1639), can be reached at (703)306-3217.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1639)

June 24, 2003

BENNETT CELSA
PRIMARY EXAMINER